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Role of medicinal plants in inhibiting SARS-CoV-2 and in the management of post-COVID-19 complications

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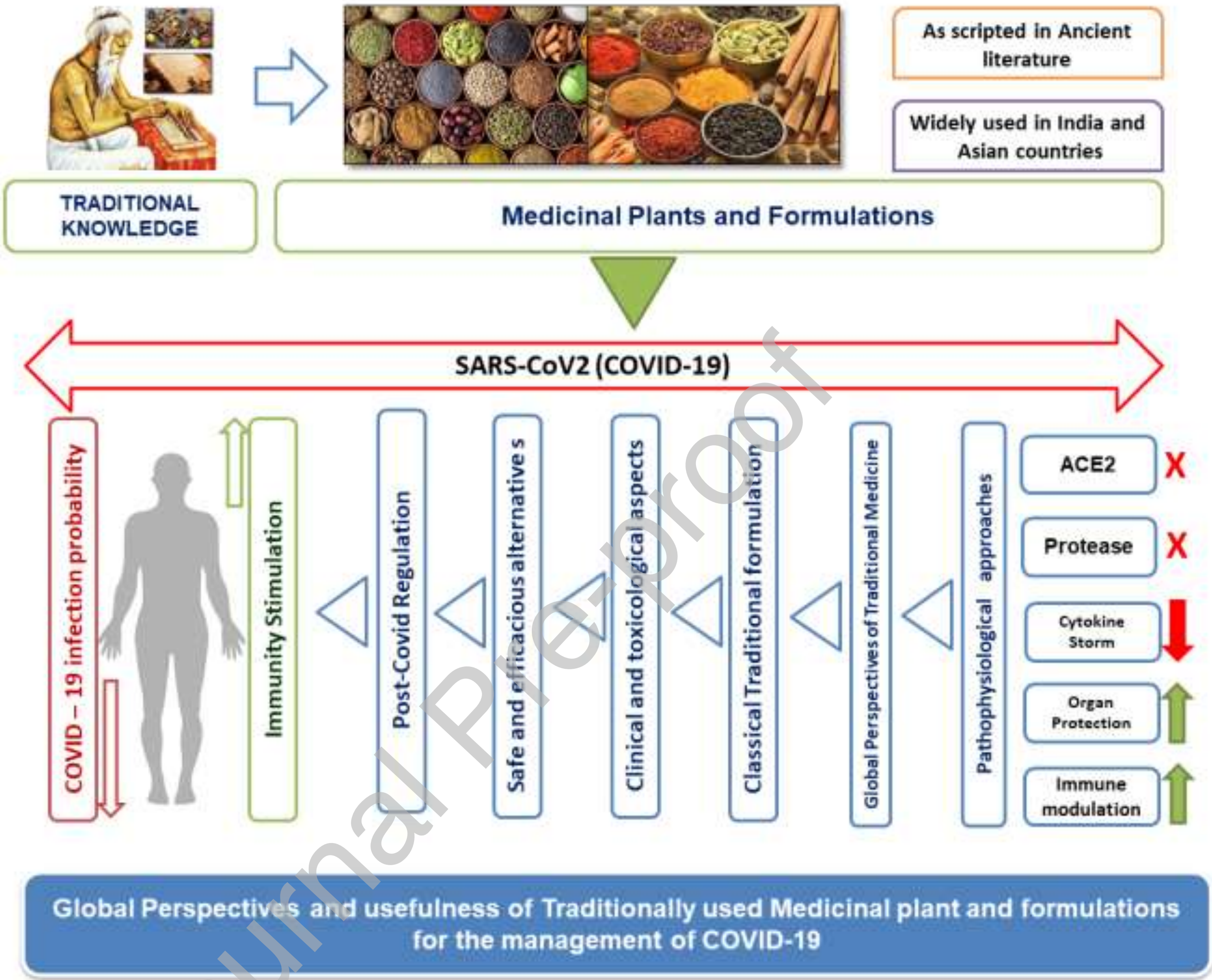
Graphical abstract



ABSTRACT

Background: The worldwide corona virus disease outbreak, generally known as COVID-19 pandemic outbreak resulted in a major health crisis globally. The morbidity and transmission modality of COVID-19 appear more severe and uncontrollable. The respiratory failure and following cardiovascular complications are the main pathophysiology of this deadly disease. Several therapeutic strategies are put forward for the development of safe and effective treatment against SARS-CoV-2 virus from the pharmacological view point but till date there are no specific treatment regimen developed for this viral infection.

Purpose: The present review emphasizes the role of herbs and herbs-derived secondary metabolites in inhibiting SARS-CoV-2 virus and also for the management of post-COVID-19 related complications. This approach will foster and ensure the safeguards of using medicinal plant resources to support the healthcare system. Plant-derived phytochemicals have already been reported to prevent the viral infection and to overcome the post-COVID complications like parkinsonism, kidney and heart failure, liver and lungs injury and mental problems. In this review, we explored mechanistic approaches of herbal medicines and their phytocomponenets as antiviral and post-COVID complications by modulating the immunological and inflammatory states.

Study design: Studies related to diagnosis and treatment guidelines issued for COVID-19 by different traditional system of medicine were included. The information was gathered from pharmacological or non-pharmacological interventions approaches. The gathered information sorted based on therapeutic application of herbs and their components against SARSCoV-2 and COVID-19 related complications.

Methods: A systemic search of published literature was conducted from 2003 to 2021 using different literature database like Google Scholar, PubMed, Science Direct, Scopus and Web of Science to emphasize relevant articles on medicinal plants against SARS-CoV-2 viral infection and Post-COVID related complications.

Results: Collected published literature from 2003 onwards yielded with total 625 articles, from more than 18 countries. Among these 625 articles, more than 95 medicinal plants and 25 active phytomolecules belong to 48 plant families. Reports on the therapeutic activity of the medicinal plants belong to the Lamiaceae family (11 reports), which was found to be maximum reported from 4 different countries including India, China, Australia, and Morocco. Other reports on the medicinal plant of Asteraceae (7 reports), Fabaceae (8 reports), Piperaceae (3 reports), Zingiberaceae (3 reports), Ranunculaceae (3 reports), Meliaceae (4 reports) were found, which can be explored for the development of safe and efficacious products targeting COVID-19.

Conclusion: Keeping in mind that the natural alternatives are in the priority for the management and prevention of the COVID-19, the present review may help to develop an alternative approach for the management of COVID-19 viral infection and post-COVID complications from a mechanistic point of view.

Keywords: SARS-CoV-2, COVID-19, traditional system of medicine, inflammatory cytokines, Immunomodulation, phytochemicals

Abbreviations:

3CL, pro-3-chymotrypsin-like protease; ACE-2, angiotensin-converting enzyme 2; AYUSH, ayurveda, yoga & naturopathy, unani, siddha and homeopathy; Bcl-xL, B-cell lymphoma-extra large; BH3, Bcl-2 homology 3; CD, Cluster of differentiation; CFR, case fatality rate; COVID-19, coronavirus disease 2019; CSIR, Council of Scientific & Industrial Research, DNA, deoxyribonucleic acid; FDA, Food and Drug Administration, IFNγ, interferon gamma, IL, interleukin; IP10, inducible protein 10; MCP1, monocyte chemoattractant protein 1; NF-κB-nuclear factor kappa-light-chain-enhancer of activated B cells; PLpro, papain-like protease; RdRp, RNA-dependent RNA polymerase; RNA, ribonucleic acid; SARS-CoV, severe acute respiratory syndrome coronavirus; TCM, traditional Chinese medicine; Th1, T helper type 1; WHO, World Health Organization

Introduction

In 2002-2003, a surveillance definition was established following the outbreak of SARS-CoV-2. At the end of December 2019, a pneumonia patient with unidentified etiology was found positive for pan-β-coronavirus which has the closest resemblance to another coronavirus, Bat CoV-RaTG13 (Zhou et al., 2020). This new virus was termed SARS-CoV-2, and the disease it causes was termed coronavirus disease 2019 (COVID-19). Whole genome sequencing analysis of clinical SARS-CoV-2 isolates from COVID-19 patients revealed a total of 104 different viral strains as of yet (Hu et al., 2021). It generally is transmitted during close unprotected contact with infected persons via virus-loaded droplets and aerosoles. Due to its novel nature, there is no immune defence present in host. Globally 178,202,610 confirmed cases of COVID-19 were reported to the World Health Organization (WHO) including 3,865,738 deaths as of June 21, 2021 (Anonymus 2021, WHO coronavirus disease COVID-19 Dashboard 2021).

The symptoms of COVID-19 are non-specific and can be asymptomatic to severe pneumonia characterized by fever, coughing, shortness of breathing and also death. Headache, fatigue, anosmia, sore throat, increased sputum production, rhinorrhea, anorexia, dyspnea, pleurisy, skin sensitivity, hemoptysis, myalgias, and diarrhea can be developed as COVID-19 symptoms (Anaya et al., 2021; Rehman et al., 2021). On a mean incubation period of 5-6 days after infection, an infected person may develop pathological symptoms such as mild respiratory complications with fever. Many case reports showed that the mortality rate increases with age, people over 80 years of age having highest mortality rate and people over 60 years of age with other disorders including diabetes, hypertension, chronic respiratory disease, cardiovascular disease, and cancer. The case fatality rate (CFR) is also higher among males compared to female individuals at any age (Anonymous, 2020a; Lee et al., 2021; Report of the WHO-China Joint Mission on Coronavirus Disease 2019).

With the outbreak of COVID-19, the uses of medicinal plant and their product or traditional herbal preparation increased dramatically around the world (Peng et al., 2020). Based on preliminary clinical reports, FDA approved chloroquine sulfate and hydroxychloroquine sulfate as first-line treatment (Gao et al., 2020; Gautret et al., 2020; Naserghandi et al., 2020). Unfortunately, these conventional drugs are not as effective against COVID-19 infection as expected (Cao et al., 2020; Ferner and Aronson, 2020).

Antiviral drugs such as favipiravir, remdesivir and kaletra (lopinavir and ritonavir combination drug) have also been put forward to improve the condition of COVID-19 patients (Guo, 2020; Mifsud et al., 2019; Sheahan et al., 2020). Drug Controller General of India approved 2-deoxy-D-glucose (2-DG) for emergency use as add-on therapy in moderate to severe coronavirus patients (Balkrishna et al., 2020a; Verma et al., 2020). However, the outcome of large randomized clinical trials was not very encouraging (Tu et al., 2020). The most common preventive and effective approach to combat the COVID-19 pandemic is the use of vaccines (Khodadadi et al., 2020). Approximately, 78 vaccine candidates have already been developed worldwide and are at different stages of clinical evaluation (Thanh et al., 2020). Up to now, several vaccine candidates are approved through Emergency Use Authorization (EUA) including the Pfizer/BioNTech Comirnaty vaccine (BNT162b2), the Oxford–AstraZeneca COVID-19 vaccine (AZD1222) sold under brand name Covishield, the Moderna (mRNA 1273) vaccine by the American Pharmaceutical and Biotechnology Company, CoronaVac by a Chinese company named Sinovac Biotech. Sinopharm in collaboration with the Wuhan Institute of Virology and Beijing Institute of Biological Products developed inactivated Chinese Corona Virus (CVC) vaccine and BBIBP-CorV, EpiVacCorona by a Russian company named Federal Budgetary Research Institution State Research Center of Virology and Biotechnology, China. Covaxin

(BBV152) was developed by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR) and National Institute of Virology (NIV). Sputnik V is a viral vector COVID-19 vaccine developed by the Russian Gamaleya Research Institute of Epidemiology and Microbiology (Logunov et al., 2021; Mishra and Tripathi, 2021). Still there are many vaccine candidates under clinical investigation. JNJ-78436735 formerly known as Ad26.COV2.S was developed by Johnson & Johnson, CanSino Biologics developed a recombinant vaccine called Ad5-nCoV and NVX-CoV2373 was developed by Novavax (Kashte et al., 2021).

1. Methodology:

Specific information on the topic was collected from the literature available from search engines such as Google Scholar, PubMed, Science Direct, Scopus, and Web of Science for retrieving published data (from 2003 to 2021) using different combination of keywords i.e., COVID-19/SARS-CoV-2, diagnosis/treatment guideline issued for COVID-19, cytokine storm, immunomodulation/anti-inflammatory/antiviral, post-COVID complications etc. The inclusion criteria limited to full text articles on pharmacological or therapeutic approaches for COVID-19 based on *in-vivo*, *in-vitro*, and *in-silico* and clinical trial reports on herbal drugs. News reports, editorial, peer review articles were also retrieved to and recent updates were included. The collected literature was electronically checked for duplicates using EndNote software. On the contrary, the exclusion criteria for the collected literature include, predatory journals source, non-english language.

2. Guidelines from different traditional system of medicine to combat COVID-19

The World Health Organization (WHO) welcomes initiatives to develop COVID-19 therapies, including drug repositioning and traditional medicines. In many countries, traditional medicine has a long history and plays an important role in healthcare. Nowadays, WHO in collaboration with several research institutions is working on the medicinal plant-based products used in traditional medicinal systems, in order to explore their scientific and clinical potential for the treatment and management of COVID-19. In many countries, WHO provided support to perform clinical COVID-19 trials for traditional medicinal products (Anonymous, 2020(b), WHO, Africa CDC push for COVID-19 traditional medicine research in Africa). The disease is almost controlled in China (Salzberger et al., 2020), but still widespread in Europe, USA, India, Brazil and other countries, which have emerged as new epicentres of COVID-19 (Grasselli et al., 2020). TCM is playing an important role to control the death rate. Along with TCM, Ayurveda might also help to manage COVID-19 (Patwardhan et al., 2020). However, there is not much solid evidence yet to prove this hypothesis. One may critically ask, why is the outbreak not under control in India, if Ayurveda would really help. The same is true for all other traditional medicines worldwide in a similar manner. Currently the data from www.clinicaltrials.gov and http://www.chictr.org.cn include 46 plant-derived phytomolecules and 64 traditional Chinese medicinal preparations are under clinical investigations targeting both management and prevention of COVID-19 viral infection. But still, it requires reliable and high-quality clinical evidence due to small sample size and long time line (Luo et al., 2020; Nile and Kai, 2021; Pang et al., 2020; Wang et al., 2021; Wei et al., 2020; Xu et al., 2020; Zhu et al., 2020). Randomized clinical trials, which reach international visibility and recognition concerning this issue, are urgently required to answer this question. The Ministry of AYUSH has come up with several preventive measures against COVID-19 infection. These preventive measures are published officially as Guidelines for Practitioners in Naturopathy, Siddha, Homeopathy, Unani, Ayurveda, Yoga and for Public Health and Health care Practitioners for COVID-19 (AYUSH Guidelines for COVID-19). The Unani system of medicine may offer potential candidates for controlling the disease burden. The textbooks of Unani medicine focused explicitly on air-borne respiratory infections. In Unani medicine, epidemics and pandemics were described with the common term *waba*, which means diseases affecting a large geographical area. Most of the Unani herbal drugs are cheap, easy to administer and easily available. As an example, vinegar is recommended made from *Saccharum officinarum* L., *Rosa damascena* Herrm., *Tamarindus indica* L., *Rheum austral* D. Don, *Viola odorata* L., *Terminalia chebula* Retz., *Cassia fistula* L. and *Punica granatum* L. (Nikhat and Fazil, 2020).

Ayurveda can prevent the disease progression by regulating the immune-inflammation state in COVID-19 patients. The Ministry of AYUSH, India, recommended different preventive measures to improve the quality of life of individual patients. Daily practice of *Yoga, Dhyana, and Pranayaam* practices may help to withstand psychological perturbations in COVID-19 patients. The use of spices such as *Curcuma longa* L., *Cuminum cyminum* L., *Coriandrum sativum* L., and *Allium sativum* L. is recommended for daily use. Consuming herbal decoctions of *Ocimum sanctum* L., *Piper nigrum* L., *Zingiber officinale* Roscoe, *Cinnamomum verum* J. Presl, *Vitis vinifera* L. are also recommended as teas to improve the immunity in COVID-19 patients. Taking *Emblica officinalis* Gaertn., *Tinospora cordifolia* (Willd.) Miers and *Tribulus terrestris* L. in equal ratio with honey suggested having benefits in post-COVID related complications. Daily consumption of ashwagandha (*Withania somnifera* (L.) Dunal) also having benefits in prophylactic care. An ayurvedic herbo-mineral preparation known as *Chyawanprasha* is also recommended due to its immunoboosting properties and in the management of post-COVID related complications. Patients with sore throat and cough are advised as steam inhalation with *Mentha arvensis* L. or *Trachyspermum ammi* L. with *Syzigium aromaticum* L. powder (Gupta et al., 2021a,b).

Based on the traditional and scientific evidence, the Ministry of AYUSH recommended the consumption of a poly-herbal decoction (*Kadha*) containing five different herbs namely, *Tulsi (Ocimum tenuiflorum L.), Dalchini (C. verum), Kalimirch (P. nigrum), Shunthi (Z. officinale) and Munakka (V. vinifera)* for boosting immunity. The network pharmacology analysis data of this immunomodulatory formulation showed to modulate several signaling pathways involved in the regulation of immunity in biological systems such as HIF-1, Estrogen, Rap1, p53, PI3K-Akt, Toll-like receptor, MAPK, cAMP, Ras, Wnt, Adipocytokine, NOD-like receptor, Chemokine, NF-κB, IL-17, TNF, Sphingolipid, and cGMP-PKG. Along with *Kadha*, it is also recommended to take *raisins* (dried *Munakka*) and golden milk (*C. longa* powder in hot milk) as a prophylactic against COVID-19 to boost immunity in the subjects with compromised immunity (Khanal et al., 2020; Schuster et al., 2017).

3. Global perspective of herbs and herbal formulae from different traditional systems of medicine to inhibit SARS-CoV-2 virus

Soon after the outbreak of COVID-19, the National Health Commission of the People's Republic of China announced a combination of TCM and commercial medicines to treat COVID-19 patients (Lin and Li, 2020). After the global spread of COVID-19, rushes for traditional herbal medications against COVID-19 have been reported in different parts of the world (Ang et al., 2020; Benarba and Pandiella, 2020; Mani et al. 2020; Mukherjee et al., 2019; Paudyal et al., 2021).

The exploration of herbs and herbal preparations used in traditional medicine, followed by bioassay-guided isolation of lead compounds from medicinal herbs, represent an attractive approach in combat this pandemic. In several African countries, home remedies are used as alternative healthcare remedies to manage COVID-19. Natural spices and leaves of medicinal plants having the antioxidant and anti-inflammatory properties were reported to be effective (Orisakwe et al., 2020).

Many natural products have broad-spectrum antiviral activity, may inhibit multiple steps in viral infection and replication and have been used in the treatment of SARS, MERS, influenza, and dengue virus. Figure S1 represents the chemical structures of the bioactive phytomolecules to be useful for the management of COVID-19 related complications. Moreover, they have been reported as immunomodulators, inhibiting inflammatory effect concerned for the significant morbidity and mortality of COVID-19 infection (Khan and Al-Balushahi, 2021; McKee et al., 2020) (Tables 1-3). Medicinal plants that showed to be effective in the management of post-COVID related complications have been tabulated in Table 4. Figure 2 represents the probable inhibition mechanism of medicinal plants/products against SARS-CoV-2 viral replication. However, the phytochemicals could be toxic at certain levels, and hence *in vitro* and *in vivo* researches are needed to evaluate the safe and therapeutic levels for each natural compound before human clinical studies can be conducted (Mani et al., 2020). Infusino et al. (2020) focuses the possible role of supplements, probiotics, and nutraceuticals in reducing the risk of SARS-CoV-2 infection or mitigating the symptoms of COVID-19 in their study.

In this Review, the importance of medicinal herbs from different traditional medicine systems together with herbs-derived secondary metabolites are summarized based on the mechanistic point of view for post-COVID related complications.

5. Herbal formulae from different traditional systems of medicine

During the first outbreak of SARS in China (2002-2003), TCM showed a great potency in reducing the fatality rate (Chen and Nakamura, 2004; Yang et al., 2020). After the outbreak of COVID-19, several TCM formulations have been frequently prescribed , *e.g., Lianhua Qingwen* capsule, *Yu Ping Feng San* decoction, *Guizhi*-and-*Mahuang* decoction, *Shuang-Huang-Lian*, *Sang Ju Yin* and *Yu Ping Feng San*, *Dang Gui Long Hui pill*, *Shufeng Jiedu* capsule, *Qingfei Paidu* decoction, *Huashi Baidu* decoction, *Huoxiang Zhengqi*, *Jinhua Qinggan* granules, *Xuebijing* injection, *Reduning* injection, *Tanreqing* injection, *Shufeng Jiedu* capsule, *Xuanfei Baidu* decoction, *Shenmai* injection and *Ma Xin Gan Shi Tang* etc (Table 2). These herbal formulations have significant antiviral, anti-inflammatory and immunomodulatory activity to combat COVID-19 (Chan et al., 2018; Ding et al., 2017; Du et al., 2014; Fu et al., 2018; Gao et al., 2014; Huang et al., 2020; Liu et al., 2015; Liu, 2020; Poon et al., 2006; Runfeng et al., 2020; Yang et al., 2020).

Based on recent updates, several herbs and isolated phytomolecules were found to inhibit the SARS-CoV-2 viral infection through different mechanisms (Table 3). Through the binding between SARS-CoV-2 spike protein and Angiotensin-converting enzyme 2 (ACE-2) receptor of the host is the major reason of viral entry into the cells of the nasal and bronchial epithelium. SARS-CoV-2 virus ingestion, replication can easily be inhibited by inhibiting human ACE-2 receptor (Galani and Andreakos, 2021). Weng et al. (2019) showed that the phenol-rich extract of *Sambucus formosana* Nakai inhibited viral replication of human coronavirus NL63. Triterpenoids and flavonoid glycosides isolated from the ethanolic extract of *Euphorbia neriifolia* L. exhibited antiviral activity against human coronavirus. The molecular docking study of isolated 3β-friedelanol showed that the friedelane skeleton could be a potential scaffold for developing new anti-HCoV-229E drugs (Chang et al., 2012). In another study, the methanol extract of *Strobilanthes cusia* (Nees) Kuntze blocked the cytopathic effect of HCoV-NL63-infected cells (Tsai et al., 2020). Mechanism based inhibition of medicinal plants/products through regulation of cytokine storm in SARS CoV-2 infection has been represented in Figure 3.

The Ministry of AYUSH in collaboration with the CSIR started clinical trials of four ayurvedic herbs with immunoboosting properties to alleviate the symptoms caused by SARS-CoV-2. These are *W. somnifera*, *T. cordifolia*, *Glycyrrhiza glabra* L. and *Piper longum* L. with AYUSH-64. This polyherbal formulation is used against malaria-related fever (*Vishamjvara*), inflammation and joint pains (Gundeti et al., 2020). Based on a clinical trial on patients with bronchial asthma, the polyherbal formulation DCBT4567-Astha-15 reduced clinical symptoms such as dyspnoea, wheezing, cough, expectoration, disability, and sleep disturbances (Murali et al., 2006). This formulation is under clinical investigation to be used against COVID-19.

6. Role of natural products in the management of post-COVID complications

6.1. Parkinsonism

SARS-CoV-2 has been detected in the brain and it has been also isolated from the cerebrospinal fluid of affected patients (Papa et al., 2020). The dynamic pro-inflammatory state of COVID-19 accompanies abnormal accumulation of α-synuclein in nerve fibres, neurons and glial cells, which leads to increased oxidative stress and causes neuro-inflammation (Achbani et al., 2020) and Parkinson’s disease symptoms. During viral infections, α-synuclein participates in the innate immune response and acts as inhibitor of viral RNA and growth in neurons (Achban et al., 2020; Chaná-Cuevas et al., 2020; McCann et al., 2014).

Bacopa monnieri (L.) Wettst. reduced dopaminergic neurodegeneration by decreasing α-synuclein aggregation and might, thus, be used as a potent anti-parkinsonian agent (Jadiya et al., 2011). *Cinnamomum zeylanicum* Blume bark and *Centella asiatica* (L.) Urb. leaves extract inhibit α-synuclein aggregation, stabilized and disintegrate the oligomers and fibrils (Berrocal et al., 2014, Kotimah et al., 2015; Shaltiel-Karyo et al., 2012). The flower petals of *Carthamus tinctorius* L. improved the behavioral dysfunction in a Parkinson's induced rat model by inhibiting α-synuclein aggregation and astrogliosis (Ren et al., 2016). The stigma of *Crocus sativus* L. inhibited the fibril dissociation and α-synuclein aggregation (Inoue et al., 2018). Crocin-1, crocin-2, and crocetin present in the extract were the major components responsible for the anti-Parkinson's effect. Leaves of *Corema album* (L.) D.Don ex Steud. promoted the formation of non-toxic α-synuclein species *in vitro* and inhibited its toxicity and aggregation in cells, by promoting the autophagic flux and reducing oxidative stress (Macedo et al., 2015). *Geum urbanum* L. inhibited α-synuclein fibrillation in a concentration-dependent way and partly disintegrated α-synuclein fibrils (Lobbens et al., 2016). The root of *Panax ginseng* C.A.Mey. prevented dopaminergic loss by attenuating α-synuclein aggregation, microgliosis and apoptosis (Van Kampen et al., 2003). The root of *Scutellaria pinnatifida* A.Ham. also attenuated α-synuclein aggregation (Sashourpour et al., 2017). *Trichosanthes kirilowii* Maxim., *Prunus japonica* Thunb., *Perillae Ramulus*, *Pogostemon cablin* (Blanco) Benth. and *Cuscuta chinensis* Lam. displayed detoxification effects on α- synuclein-induced damage in a yeast model of Parkinson's disease (Fu et al., 2014; Sohn et al., 2012). The alkaloid acetylcorynoline from *Corydalis bungeana* Turcz. reduced α-synuclein aggregation leading to decreased lipid peroxidation which also maintained efficient cellular signaling (Follmer, 2020). Curcuminoids prevented neuroinflammation by reducing pro-inflammatory cytokine levels (Ojha et al., 2012). Medicinal plants that showed to be effective for the mangement of post-COVID complications have been represented in Table 4.

Olfactory dysfunctions are very common among COVID-19 patients. A considerable portion of patients experienced with the loss of smell and taste, while one third additionally suffered from rhinitis. Hyposmia is a common non-motor symptom of early stages of Parkinson's disease (Bocksberger et al., 2020; Xiao et al., 2014). Hyposmia without nasal dysfunction and rhinorrhea was also documented (Giacomelli et al., 2020; Lechien et al., 2020; Lovato and Filippis, 2020).

6.2. Mental problems

SARS-CoV-2 can appear as being both neuro-invasive and neuro-virulent. One in every three patients recovering from COVID-19 suffers from neuropsychological problems ranging from headache, dizziness, memory disorder, seizures, depression and lingering loss of smell or taste to mood disorders and deeper cognitive impairment. Those patients with insomnia feature stress, anxiety, depressive symptoms, denial, anger, mental breakdown, and those with pre-existing mental illness experience worsening of their conditions (Ananya et al., 2021; Czeisler et al., 2020; Roy et al., 2021; Schäfer et al., 2020). The demyelination syndrome troubles COVID-19 patients, in which the protective coating of nerve cells is attacked by the immune system. This is an autoimmune disease causing weakness, numbness, tingling, spurring psychosis and also hallucinations (Coony, 2020).

COVID-19 patients are challenged by severe stressors, including fear of death from life-threatening illness, pain from medical interventions, endotracheal intubation, limited ability to communicate, and the feeling to loose control (Kaseda and Levine, 2020). The Chicago medical center reported that more than 40% of COVID-19 patients exhibited neurologic manifestations and more than 30% of those had impaired cognition. Sometimes, the neurological manifestations can be calamitous and can even lead to death.

Implementation of Indian herbs and herbal formulations such as Brahmi (*B. monnieri*), Shankhpushpi (*Convolvulus prostratus* Forssk.), Giloy (*T. cordifolia*), Malkangni (*Celastrus paniculatus* Willd.), Tulsi (*O. tenuiflorum*), Ashwagandha (*W. somnifera*) etc. can help managing psychological post-COVID conditions. Bacoside from *B. monnieri* induced an antioxidant environment in brain, and its neuroprotective activity was attributed to the regulation of mRNA translation and surface expression of AMPA, NMDA and GABA neuroreceptors in the brain. *Acorus calamus* L. is another plant, which is used as nerve tonic, tranquilizer, sedative etc. by reducing AChE levels and interaction with GABA receptors. It showed antidepressant properties by induction of α1, α2 and 5-HT_{1A} receptors. Flowers of *Convolvulus pluricaulis* Choisy showed anxiolytic activity and are also used as brain tonic in mental aberration and neurosis. The plant possesses strong antioxidant activity towards brain cells. It also inhibited AChE and 5-LOX, which are involved in neurodegenerative disorders. The seed oil of *C. paniculatus* exhibited significant antidepressant-like effects by interaction with dopamine D_2 receptors, serotonergic and $GABA_B$ receptors. It also inhibited MAO-A and caused reduction in plasma corticosterone levels (Joshi and Pandya, 2020).

TCM plants including Lily bulb, *Rehmannia*, *Anemarrhenae* and *Ganmai Dazao* decoctions were incorporated to treat depression. *G. Dazao* decoction was used to treat hysteria, whose symptoms were sadness, crying, mood disorders, and abnormal behaviour. It is composed of *G. glabra*, *Triticum aestivum* L. and *Ziziphus jujuba* Mill. According to the TCM theory, this decoction nourishes *Yin* of heart and calms mind (Ma et al., 2020). *G. Dazao* decoction combined with Lily bulb and *Rhizoma Anemarrhena* decoction is also used to treat depression, which effectively reduced the depression symptoms of patients and improved their sleep status. This modified *G. Dazao* decoction is clinically efficient and safe in the treatment of perimenopausal patients with severe depression, because of the regulation of monoamines and aminoacid neurotransmitters, regulation of immune inflammation, and also the reduction of the level of inflammatory factors (Li and Gao, 2014).

Suanzaoren decoction, *Huang lian E jiao* secoction, *Zhizi Chi* decoction were also incorporated in the drug treasure trove to treat the anxiety of internal heat and *Yin* deficiency syndrome. *Suanzaoren* decoction is made from *Ziziphus spinosa* Hu, *liquorice* root, *R. Anemarrhena*, *Poria cocos* (Schw.) and *Chuanxiong Rhizoma*. *Huang lian E jiao* decoction is composed of *Coptidis Rhizoma*, *Scutellariae Radix*, *Paeoniae Radix Alba*, *Colla Corii Asini* and fresh egg yolk. The anti-anxiety properties of the *Suanzaoren* decoction was related to an increased NO concentration in the blood and the decrease of IL-1β and TNF-α level in serum (Wang and Xie, 2004; Liu, 2018). In another study, the combination of *Suanzaoren* decoction and *Zhizi Chi* decoction was significantly improved anxiety-related insomnia (Liu et al., 2014). The anti-anxiety activity of *Suanzaoren* decoction and *Huanglian E jiao* decoction was related to elevated γ-GABA levels (Zhao, 2012). Lily bulb, *Rehmannia* decoction and *Guilu Erxian* decoction were useful against post-traumatic stress disorder (PTSD; internal heat and *Yin* deficiency syndrome) by regulating synaptic plasticity, anti-apoptosis, anti-inflammation and reducing fear memory (Li et al., 2020).

6.3. Kidney failure

The CDC reported that of the adults hospitalized for COVID-19 with underlying conditions in USA, 74.8% had chronic renal disease, but patients with chronic renal disease consisted of only 3% of the total cases (Abbott, 2020). A recent clinical study with 701 patients from a hospital in Wuhan found that 5.1% of patients admitted for COVID-19 developed acute kidney injury (Cheng et al., 2020). During the infection, the virus circulated in the blood to reach the kidney and caused damage to renal resident cells, which was manifested by proteinuria, hematuria, and elevated levels of blood urea nitrogen, serum creatinine, uric acid as well as D-dimer (Cheng et al., 2020; Henry and Lippi, 2020; Li et al., 2020). The mortality rate of COVID-19 patients with AKI was significantly higher (5.3 times higher in acute kidney injury than 1.5 times in chronic illnesses) (Alberici et al., 2020; Su et al., 2020; Xu et al., 2020). The main binding site for SARS-CoV-2 is the ACE2 protein, which is expressed in the kidney much more than the lungs (Serfozo et al., 2020; Ye et al., 2006). Targeting of ACE2 by SARS-CoV-2 results in angiotensin dysregulation, innate and adaptive immune pathway activation, and hyper-coagulation to result in organ injury and AKI associated with COVID-19. SARS-CoV-2 might cause tubular damage through infiltrating renal parenchyma by an exaggerated and often uncontrolled surge of plasma pro-inflammatory factors (IL2, IL7, IL- 10, GSCF, IP-10, MCP-1, MIP1A and TNF-α) known as ‘‘cytokine storm’’ (Wen et al., 2020). Inflammatory cells such as $CD68^+$ macrophages, $CD4^+$ T cells, and $CD56^+$ natural killer cells can be present in tubulointerstitium of affected patients. The hyper-activation of these immune cells may eventually promote fibrosis, induce epithelial cell apoptosis, and cause microvasculature change. Moreover, C5b-9 complex expression and disposition on tubular cells causes renal interstitial damage (Diao et al., 2020; Rodríguez et al., 2018; Saffarzadeh et al., 2012).

Thirty-eight patients with moderate chronic renal failure were treated with 1 g *Rheum palmatum* L. (Chinese *rhubarb*) root extract *per* day, which led to significant decreases in serum BUN and creatinine level (Sanada, 1996). Tincture of *lespedeza* (*Lespedeza capitata* Michx.) showed beneficial effect in patients with acute and chronic renal failure (Yarnell et al., 2007). The effect may be due to the compound proanthocyanidins present in the plant extract showing angiotensin-converting enzyme (ACE) inhibition effects (Wagner and Elbl, 1992). A study showed that

Urtica dioica L. seed might be an effective herbal treatment for renal failure patients, as it lowers the serum creatinine levels and also reduces the symptoms (Treasure, 2003). Roots of *Andrographis paniculata* (Burm.f.) Nees significantly reduced blood proteinemia and uremia (Rao, 2006). *Rheum officinale* Baill. combined with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and and Chinese patented medicine *Rheum* (CPM-Rheum) might be used to improve the condition of impaired renal function (Yang et al., 2018).

6.4. Heart failure

Some patients having problems related to heart even exhibited signs related to mild to severe heart damage in post-COVID infection due to an overactive immune response with abnormal heart rhythms, heart muscle disease and also heart failure in severe cases of myocarditis (Sharma, 2020). A report of the University of Frankfurt in Germany showed that more than 78% patients exhibited cardiac issue and 60% patients, who had COVID-19, exhibited cardiac inflammation (Puntmann et al., 2020). In severe cases, elevated troponin levels in the blood were seen in infected patients. Multi-drug therapy may cause serious cardiovascular complications due to drug-drug interactions. The antiviral drug remdesivir reduced blood pressure and caused unusual heart rhythm (Citroner, 2020; Healthline.com; https://www.healthline.com/health-news/how-covid-19-may-damage-your-heart).

The ACE2 receptor plays an important role in regulating blood vessel dilation and blood pressure. The anti-hypertensive therapy could raise the number of ACE2 receptors expressed on cells, generating more molecular gates for SARS-CoV-2 to enter (Pesheva, 2020). In Ayurveda, *Rasayana* acts as antioxidant, anti-stress, anti-inflammatory drug and improves the cardiac health of patients (Rastogi et al., 2020). Cucurmin from *C. longa* blocked cytokine release, specifically

IL-1, IL-6, pro-inflammatory cytokines and TNF-α possesses anti-inflammatory activity in COVID-19 patients (Khanna et al., 2021). Naringin, naringenin and hesperidin present in *Citrus* sp. inhibited the expression of pro-inflammatory cytokines in macrophages, restrained cytokines via inhibiting HMGB1 expression and obstructed binding affinity of the ACE 2 receptor to the coronavirus (Cheng et al., 2020). *G. glabra* root also exhibited anti-inflammatory properties, which induces interferon production in the body and prevents heart disease. *Cannabis sativa* L. shows anti-inflammatory actions by modulation of expression of ACE2 and the serine protease TMPRSS2, which is a pre-requisite for SARS-CoV-2 invasion into host cells. Triterpenoids and flavonoids in *Glycyrrhizae radix* is used as anti-inflammatory and cardioprotective drug. *Aconiti lateralis* radix praeparata was widely used to treat heart failure in COVID-19 patients (Ang et al., 2020). For cardiovascular and circulatory disorders, *Salvia miltiorrhiza* Bunge and *T. terrestris* can be used in infected and recovered patients (Benarba and Pandiella, 2020). *Uncaria tomentosa* (Willd. ex Schult.) DC. exhibited immunostimulating and cardiovascular protective activity. *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. possesses anti-inflammatory and antioxidant effects by inhibition of the TLR4/NF-kB/NLRP3 pathway in murine alveolar macrophages (Firenzuoli et al., 2020). *P. longum* contains phenanthrenes, phenylpropanoic acids, diarylheptanoids, piperidines, oxanes showing cardioprotective activity. *T. cordifolia* is well known for its cardiotonic activity and is used to treat heart diseases (First Report and Reccomendation, 2020, ayush.gov.in).

6.5. Liver injury

Some studies reported higher serum pro-inflammatory cytokine and chemokine levels in infected patients with abnormal liver function (Duan et al., 2003; Feng et al., 2020; Li et al., 2020). Hepatic cells can be directly infected due to the ACE2 expression in the liver, bile duct cells and cholangiocytes, which may explain dysregulated liver function in COVID-19 patients (Chai et al., 2020; Hamming et al., 2004). Liver biopsies in infected patients showed a significant increase in mitotic cells and ballooned hepatocytes, causing apoptosis of liver cells (Chau et al., 2004). The SARS-CoV-specific protein 7a affects the liver tissue by inducing apoptosis via a caspase-dependent pathway (Tan et al., 2004).

Besides, application of high-dose antibiotics along with hepatotoxic antiviral drugs and steroids led to liver abnormalities and liver injury in 76% of COVID-19 patients (Ali, 2020), as documented by elevated serum levels of ALT, AST, GGT, and TB (Cai et al., 2020; Guan et al., 2020; Zhang et al., 2020a,b; Zhao et al., 2020). Pre-existing liver disease among COVID-19 patients showing comorbidities such as hypertension (68%) and diabetes (48%) increased the risk of mortality (Singh and Khan, 2020; Zhang et al., 2020a).

T. cordifolia (leaf, stem and root), *Momordica charantia* L. (fruit), *M. arvensis* (leaves), *Lawsonia inermis* L. (leaves), *E. officinalis*, *Eclipta alba* (L.) Hassk. (leaves), *Clitoria ternatea* L. (leaves), *Cassia angustifolia* M. Vahl (leaves), *Argemone mexicana* L. (leaves), *Abrus precatorius* L. (seeds) normalized elevated levels of AST, ALT, ALP and bilirubin *in vivo* (Battu and Kumar, 2009; Beedimani and shetkar, 2015; Bhuvaneswari et al., 2014; Kavitha and Geetha, 2018; Kowti et al., 2013; Mohamed et al., 2017; Nithianantham et al., 2011; Shanmugasundaram et al., 2010; Sourabie et al., 2012; Zahra et al., 2012). The fruits of *Solanum xanthocarpum* Schrad. & H. Wendl. normalized the serum parameters (SGOT, SGPT, ALP, TB) better than *Juniperus communis* L. fruit in paracetamol- and azithromycin-induced liver toxicity in rats (Singh et al., 2015).

6.6. Lung injury

The heterogeneity of the clinical COVID-19 presentation has prompted the conceptualization of novel paradigms to individualize clinical management of COVID-19 (Gattinoni et al., 2020). The Berlin Criteria define the acute respiratory distress syndrome (ARDS) by acute hypoxaemic respiratory failure following an acute event (such as viral respiratory infection) that presents as bilateral pulmonary infiltrates on lung imaging in the absence of a purely cardiogenic or hydrostatic etiology (Ranieri et al., 2012). Nevertheless, a recent cohort study reported that 85% ICU patients with COVID-19 meet the Berlin Criteria definition of ARDS and that is a well-established supportive intervention for ARDS, such as low tidal volumes and prone ventilation, resulted in significant improvement in oxygenation and lung compliance (Ziehr et al., 2020). Mortality attributable to SARS-CoV-2 infection occurs mainly through the development of viral pneumonia-induced ARDS.

The virus could cause lung parenchymal injury resulting in pneumonitis barring interstitial lung and/or alveolar inflammation features. Also, the virus could directly bind to the ACE-2 receptors facilitating endothelial dysfunction. The deregulated inflammatory response of cells (*e.g.*, polymorphonuclear neutrophils, macrophages, vascular endothelial cells and alveolar epithelial cells) activated the production of pro-inflammatory factors (*e.g.*, TNF-α, IL-1, IL-9 and IL-8), inflammatory mediators (*e.g.*, elastin, cathepsins, collagenases and gelatinases, cytokines, chemokines) and other inflammatory transmitters, which cause damage to the alveolar epithelial cells. The associated cytokine release syndrome could exacerbate both lung parenchymal and microvascular inflammation, promoting refractory forms of ARDS with associated hypercoagulable states and microthrombosis (Klok et al., 2020; Tang et al., 2020; Zhang et al., 2020c). Several signal transduction pathways such as NF-κB, mitogen-activated protein kinase (MAPK), nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3 (NLRP3), toll like receptors (TLRs), adrenergic receptors and JAK/STAT signaling pathways are involved in this inflammatory process (Chang et al., 2018; Li et al., 2019; Sun et al., 2018a). Hence, it can be stated that the COVID-19-associated cytokine release syndrome may be the catalyst of two parallel inflammatory pathways: one promoting parenchymal lung injury and another one facilitating thromboembolic phenomena, resulting in a “dual-hit” lung injury (Fraissé et al., 2020; Hékimian et al., 2021; Menter et al., 2020). Another cause is lung edema and lung dilatation due excess production of reactive oxygen species (ROS), which cause damage to the cell membrane by unsaturated fatty acids (Fu et al., 2017; Imai et al., 2008). Several plant-derived phytomolecules were reported to be effective in acute lung infection through modulation of NF-κB, MAPK and Nrf2 signaling pathways owing to their anti-inflammatory and anti-oxidant activities (He et al., 2021).

7. Discussion

Traditionally used Indian medicinal herbs/herbal preparations are promising candidates for the treatment and management of various illnesses through rejuvenating human wealth (Gomathi et al., 2020; Mukherjee et al., 2017). Ayurveda and Siddha practices are still widely used among the Indian population for maintaining human well-being (Mukherjee et al., 2019). By identifying certain phytocompounds, it is possible to effectively characterize medicinal herbs that could help to alleviate the SARS-CoV-2 viral infection. Hence, by repurposing Indian medicinal plants, more innovative treatment options can be penned down to defeat this viral pandemic and post-COVID related complications (Balachandar et al., 2020). In this review, we systematically summarized and analyzed the pharmacological importance of herbs and herbs-derived secondary metabolites which may be effective against COVID-19 related infections and by the traditional practice recommended by all available guidelines.

Several therapeutic strategies were put forward for the development of treatments against COVID-19 from the pharmacological point of view such as antivirals (*e.g.*, ribavirin, sofosbuvir, lopinavir/ritonavir, remidesivir, favipiravir etc.) (De Clercq, 2007) and antimalarials (hydroxychloroquine) (De Clercq, 2009), anti-inflammatory drugs (*e.g.*, baricitinib) (Stebbing et al., 2020), and monoclonal antibodies (Zheng and Song, 2020). In China, three patent herbal drugs, *Lianhuaqingwen* capsules and *Jinhuaqinggan* granules for mild conditions and *Xuebijing* (injectable) for severe conditions were approved to treat COVID-19 symptoms. These herbal formulations can effectively relieve symptoms, such as fever, cough, and fatigue, and reduce the probability of patients developing severe conditions (A report by National Health Commission of Chinese). Glycyrrhizin from liquorice root is the most frequently used Chinese herb, which inhibited the replication of clinical isolates of the SARS virus (Cinatl et al., 2003). *T. cordifolia* aqueous extract twice a day for 15 days can be effective against chronic fever, provided by AYUSH, Government of India as therapeutic approach against COVID-19 (Vellingiri et al., 2020). AYUSH also suggested that the extract of *Eupatorium perfoliatum* L. may be helpful to treat COVID-19-related respiratory symptoms (Vellingiri et al., 2020). After the acute phase of COVID-19, majority of the patients developed persistent and prolonged clinically significant physical and mental adverse outcomes affecting the quality of life. It was observed that such adverse outcomes were not confined; rather it is recognized as a multi-organ disease and increased risk of indolent death (Oronsky et al., 2021). The reviewed data shows that *A. paniculata*, *Cassia tora* L., *Phyllanthus emblica* L., *G. glabra*, *Azadirachta indica* A.Juss., *Morus alba* L., *P. longum*, *Nigella sativa* L., *Camellia sinensis* (L.) Kuntze, *U. dioica*, *C. longa*, *T. terrestris*, *Chrysanthemum indicum* Thunb., *Astragalus propinquus* Schischkin, *S. miltiorrhiza*, *Salvia officinalis* L., *C. zeylanicum*, *P. nigrum*, *Z. officinale*, *Mucuna pruriens* (L.)

DC., *Psoralea corylifolia* L., *Ecklonia cava, T. cordifolia*, *Syzygium aromaticum* (L.) Merr. & L.M.Perry, *W. somnifera* were found to have enriched biological benefits due to their varied secondary metabolites. This may provide a more rational phytotherapeutic choice to improve the general well-being effectively by counteracting the biological complications caused by for patients affected with COVID-19.

8. Conclusion and perspectives

As a matter of fact, the pandemic is far from over. There are more questions than answers about diagnosis, treatments, and, what we need most, effective cures and aftercare. This review may serve as reference in traditional herbal medicine for COVID-19 treatment. The present review compiled pharmacological information of more than 50 herbal medicines, which potentially combat the viral infection and post-COVID complications through different mechanisms. Most information is rather based on some *in-vitro* and *in-silico* investigations and anecdotal clinical data. The basic molecular mechanisms are also unexplored yet.

It should be noted that there is still no convincing clinical evidence on the activity of most herbal products. Unlike modern medicines, herbs are often claimed to be non-toxic, due to their natural origin and long-term use as traditional medicines. However, numerous difficulties can be occurred due to the adulteration, substitution, contamination, misidentification, intrinsic toxicity, drug-herb interactions and lack of standardization. For that reasons, pre-clinical evaluation of therapeutic effectiveness is a great concern for the further development of safe and effective herbal treatments. As the COVID-19 pandemic continues, substantial progress has been made in pathogen monitoring, identifying sources, basic etiology, and clinical treatment. Herbs from traditional system of medicine may be useful in alleviating the disease symptoms but it requires more research works to unravel their therapeutic potential. The integration of traditional medicine into conventional treatment may be an alternative approach for the treatment of COVID-19 in the future. However, the global situation is very serious, and numerous questions remain unanswered. It will take combined efforts of traditional and western medical systems worldwide to ultimately extinguish this pandemic.

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Conflict of interest:

The authors declare that there is no conflict of interest.

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Tables and Figure:

Table 1. Herbs found to be effective against COVID-19 through *in-vivo*/ *in-vitro* analysis

Table 2. Herbs derived secondary metabolites found to be effective against COVID-19 through molecular docking analysis

Table 3. SARS-CoV-2 inhibition potential of herbs from traditional formulation through evidence based approaches

Table 4. Medicinal plants to be useful for the management of post-COVID complications

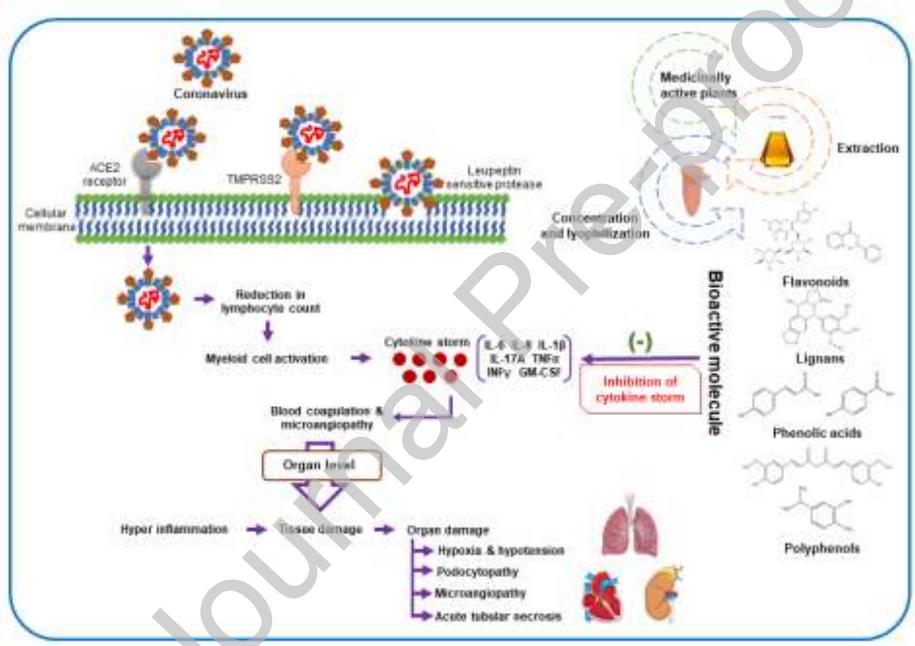

Figure 2. Probable inhibition mechanism of medicinal plants/product against SARS CoV-2 viral replication.

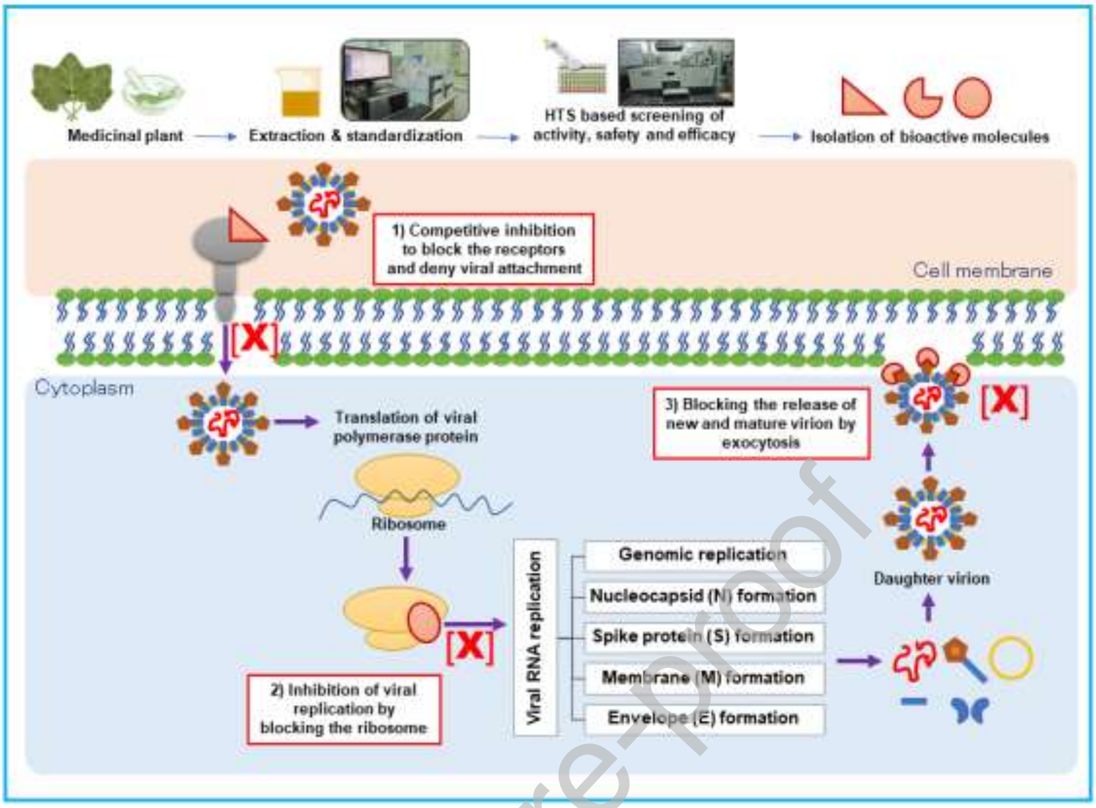

Figure 3. Mechanism based inhibition of medicinal plants/product through regulation of cytokine storm in SARS CoV-2 infection.

Declaration of interests: None

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Table 1. Herbs found to be effective against COVID-19 through *in-vivo*/ *in-vitro* analysis

Plant Family	Plant name	Antiviral	Anti-inflammatory	Immunomodulation	References
***In-vitro*/*in-vivo* assays**					
Acanthaceae	*Andrographis paniculata* (Burm.f.) Nees	Binding potential with active residues of ACE2 that mediate host viral interface	Andrographolide reduces the levels of inflammatory cytokines TNFα, IL-12, IL-1β, IL-6, IL-18 in LPS/ IL-4-activated murine macrophages	Andrographolide significantly stimulate the immune response, regulate the production of NK cells and cytokines and stimulate the production of cytotoxic T-lymphocytes	Lu et al., 2019; Wang et al., 2010; Varma et al., 2011; Dhanasekaran and Pradeep, 2020
Amaryllidaceae	*Allium sativum L.*	Aqueous bulb extracts and essential oils restrained viral protease enzyme by inhibiting amino acid synthesis	Allicin inhibit of TNF-induced secretion of IL-1β, CXCL8 and IP10	Crushed garlic extract increase the production of IFNγ and expansion of CD4+ T-cells	Mohammadi and Shaghaghi, 2020; Lang et al., 2004; Arreola et al., 2015
Anacardiaceae	*Rhus chinensis* Mill.	Ethanol extract of gall having the inhibitiory activity of SARS-CoV virus into host cell and prevented virus replication Tetra-O-galloyl-β-d-glucose showed to inhibit SARS	Aqueous extract inhibits the production of inflammatory cytokine IL-6 *in-vivo*	Aqueous extract inhibits IL-10 expression and act as immunomodulator	Yi et al., 2004; Djakpo and Yao, 2010; Kai et al., 2018; Sun et al., 1018b

		CoV			
Asteraceae	*Echinacea purpurea* L.	Herb and roots ethanol extract act against some viruses with a membrane through direct virucidal activity	Unpurified fresh pressed juice mediated the increased release of various cytokines, including IL-1, IL-10,and TNF-α by macrophages	Crude polysaccharides act as immunostimulator	Sharma et al., 2009; Burger et al., 1997
Brassicaceae	*Isatis indigotica* Fortune ex Lindl.	Methanol root extract exhibited antiviral activity against Japanese encephalitis virus. An arabinogalactan isolated from the root showed antiviral activity against H1N1 influenza vaccine or hepatitis B surface antigen	Tryptanthrin was found to have anti-inflammatory activity. Topical administration of extracts significantly inhibited the ear oedema and paw oedema induced by carrageenan	Polysaccharides fraction promoted humoral immune response of the body and produces immune effect on KM and Balb/c mice respectively	Chang et al., 2012b; Shan et al., 2015; Chen et al., 2021; Ho and Chang, 2002; Hamburger, 2002
Caesalpinaceae	*Cassia tora* L.	Ethanol seed extract inhibits 3CL protease and SARS CoV replication. The anti-viral activity measured by cell-based on Vero E6	Ethanol seed extract induces expression of phosphorylated cAMP response		Islam et al., 2020; Wen et al., 2011

		cells			
Calophyllaceae	*Calophyllum blancoi* Planch.	Blancoxanthone and pyranojacareubin from the root exhibited antiviral activity against HCoV 229E virus	Extracts from leaves and roots showed anti-inflammatory and anti-nociceptive activity in mice model		Shen et al., 2005; Filho et al., 2009
Celastraceae	*Tripterygium regelii* Sprague	Triptofordin C-2 showed antiviral activity against HSV-1, HCMV, measles virus and influenza A virus	Dichloromethane and ethyl acetate fractions of herbs induced IL-8 in LPS-activated rat macrophages	Tripterygiumine I and tripterygiumine Q isolated from root extract exhibited immunosuppressive activity against human peripheral mononuclear cells	Hayashi et al., 1996; Lee et al., 1995; Lv et al., 2019
Cibotiaceae	*Cibotium barometz* (L.) J. Sm.	Methanol and ethanol extract of dried rhizome inhibit viral replication, levels of spike protein and SARS-CoV 3CL protease activity	The methanol extract of rhizome suppressed NO and IL-6 and also decreased iNOS and COX-2 expression		Wen et al., 2011; Wu and Yang. 2009
Compositae	*Chrysanthemum indicum* L.	The herb found to inhibitory SARS	Flower and bud ethanol extract	Inflorescence or bud ethanol extract	Kwong et al., 2020; Lee et al., 2009;

		CoV-2 virus	reduced TNF-α, IL-6 and IL-1β production	significantly increased delayed-type hypersensitivity reaction, enhanced antibody generation by splenic cells and IgG and IgM levels	Cheng et al., 2005
Dryopteridaceae	*Dryopteris crassi rhizoma* Nakai	It clear heat and detoxify, removes lung hotness and having potent against SARS CoV-2	Ethanol root extract diminishes the production of NO and PGE2, down regulate the iNO synthase, COX-2, and TNF-a mRNA expression and also decrease the level of IL-6	Bioactive compound of isolated from rhizome extract exhibit immunomodulatory activity by replicating IL-1β, TNF-α	Yang et al., 2020; Yang et al., 2013; Cheng et al., 2016
Fabaceae	*Mucuna pruriens* (L.) DC.	Peptide fraction has been reported in the treatment of to liver cancer, HCV, and high activities of protecting DNA damages	Essential oil from leaf and flavonoids from seed powder showed anti-inflammatory	The bean extract showed immunomodulatory activity by modulating TNF-α, IL-6, IFN-l, IL-1b, iNOS and IL-2 level in the CNS and also enhanced the activity of the transcription factor NF-kB	Taghizadeh et al., 2021; Avoesh et al., 2020; Javed et al., 2010; Mallurwar et al., 2006; Rai et al., 2017
	Glycyrrhiza glabra L.	Glycyrrhizin (i) was shown to	Glycyrrhizic acid, liquiritin and	Glycyrrhizin enhanced proliferation of allogenic	Cinatl et al., 2003; Hoever et al., 2005;

		inhibit SARS-coronavirus (SARS-CoV) replication	liquiritigenin inhibited iNOS, COX-2, TNF-α, IL-1β and IL-6. The root extract also inhibited the expression levels of TNF-α, IL-1β and IL-6	T cells along with the production of IFN-γ and IL-10 and reduced IL-4 production	Fiore et al., 2008; Bordbar et al., 2012
Gentianacee	*Gentiana scabra* Bunge	n-hexane extract of rhizome inhibited SARS-CoV replication in cell-based cytopathogenic effect	Chloroform and methanol extract of rhizomes and roots inhibit production of IL-6 and NO	Polysaccharide fraction the aqueous root extract increased lymphocyte proliferation	Yang et al., 2010; Wen et al., 2011; Wang et al., 2014; He et al., 2015
Lamiaceae	*Hyptis atrorubens* Poit.	Methyl rosmarinates inhibited 3CLpro of SARS-CoV-2 virus	Suaveolol and methyl suaveolate isolated from the methanol leaf extract showed anti-inflammatory activity in croton oil ear edema model		Qamar et al., 2020; Grassi et al., 2006
	Salvia miltiorrhiza Bunge	Ethyl acetate and water extract of root showed antiviral activity against enterovirus 71by interrupting	The polysaccharides extract inhibited mRNA transcriptions of TNF-α, IL-6, iNOS, and COX-2 and protein expressions of NF-	Polysaccharides extract enhanced expression of *IL-4, IL-6,and IFN-γ*	Liu et al., 2013; Chen et al., 2017; Han et al., 2018; Wu et al., 2007

		viral RNA synthesis and viral entry	κB, p-p65, and p-IκBa in LPS stimulated RAW264.7 cells		
	Salvia officinalis L.	Essential oils from fruits was found to be active against SARS-CoV and HSV-1 replication	Flavonoids isolated from fresh leaves and flowers reduce inflammation in the mouse carrageenan model. It's major constituent caffeic acid decrease the IL-6 level	The polysaccharide fractions showed immunomodulatory activity	Loizzo et al., 2008; Ghorbani and Esmaeilizadeh, 2017; Capek et al., 2003
	Scutellaria baicalensis Georgi	Baicalein (iv) inhibits 3CLpro, PLpro activity, RdRp and SARS-CoV-2 replication. Chrysin (v) inhibited PLpro Chrysin-7-O-β-glucuronide, Cosmosiin inhibited 3CLPro	The root aqueous extract inhibited the production of NO, IL-3, IL-6, IL-10, IL-12p40, IL-17, IP-10	Baicalin suppresses TNF-α, IL-6 and IL-12p70 secretion and expressions of CD80, CD86 and MHC II	Liu et al., 2021; Wu et al., 2020; Yoon et al., 2009; Lin et al., 2017
	Scutellaria barbata D. Don	Flavon rich extract and aqueous root inhibit parainfluenza-virus-type-1 infection and	In lipopolysaccharides stimulated RAW264.7 cells the ethanol and ethyl acetate root extracts inhibit the	In Lewis-bearing C57BL/6 mice model aqueous root extract decreased levels of IL-17, IL-10, FOXP3, TGF-β1, RORγt, and IL-6 and	Liu et al., 2018; Guo et al., 2009; Gong et al., 2015; Shang et al., 2010

		respiratory syncytial virus	production of iNO, PGE2, IL-6, and IL-1β	increasing the levels of IL-2 and IFN-γ	
Lauraceae	*Cinnamomum zeylanicum* L.	Butanol extract of bark inhibited SARS CoV virus	Methanol bark extract showed anti-inflammatory activity in *in-vivo* animal models	Polyphenolic fractions of bark extract stimulate lymphocytes proliferation, immunoglobulin production and IL-1β production. The oil and bark extract having immunosuppressive potential	Zhuang et al., 2009; Kubo et al., 1996; Balekar et al., 2014
	Laurus nobilis L.	Essential oils inhibited SARS-CoV and HSV-1 replication *in vitro*	Hydro-alcoholic extracts of leaves and seeds showed anti-inflammatory activity in mice	Essential oils of leaves shows immune stimulatory activity by decrease in the hematocrites: HCT, hemoglobin (HGB) and increase the level of white blood cells	Loizzo et al., 2008; Esra et al., 2007
Leguminosae	*Psoralea corylifolia* L.	Ethanol seed extract inhibit SARS virus replication acting on papain-like protease (PLpro)	Bakuchiol inhibited the expression of iNOS in RAW 264.7 macrophages cells	Ethanol seed extract having immunostimulant activity and increases cell mediated and humoral immune responses	Mohamed et al., 2017; Pae et al., 2001; Kim et al., 2014
Lessoniaceae	*Ecklonia cava*	Phlorotannins from ethanol extract	In LPS stimulated RAW 264.7 cells	In an *in-vivo* model the enzymatic extract having	Kwon et al., 2013 Cho et al., 2019

		exhibited antiviral property against porcine epidemic diarrhea virus, influenza A viral strains (H1N1 and H9N2)	ethanol extract of reduced NO, PGE2 level and downregulated TNF-α, IL-1β, and IL-6 gene expressions	immunomodulatory effect by enhancing the mRNA expression and production IL-4 and IL-1. It also reduced TNF-α and IFN-γ level	Kim et al., 2019 Ahn et al., 2008
Loranthaceae	*Taxillus chinensis* (DC.)	Stem and leaf hexane extract inhibit viral replication in SARS-CoV-infected Vero E6 cells	Aqueous stem extract inhibits the production of NO and TNF-α and possesses anti-inflammatory activity	Polysaccharide fraction enhanced TNF-α and NO production	Zhang et al., 2013; Wen et al., 2011; Wen et al., 2011; Ding et al., 2013
Meliaceae	*Azadirachta indica* A. Juss	Nimboloid (terpenoid lactone) is effective in regulating the ARDS, is a key pathological feature of COVID-19	Quercetin (i) from leaf methanol extract showed anti-inflammatory activity by the inhibition of TNF-α	Flowers aqueous stimulated both specific and non-specific immune responses, humoral and cell mediated response Nimbin (constituent of neem oil) exhibited immunomodulatory activity by potentiate phagocytic activity, antigen-presenting ability of macrophages and enhances IL-1, IFN-Γ, and TNF-α production	Shetty et al., 2020; Schumacher et al., 2011; Shah et al., 2009; Das, 2021
	Toona sinensis (Juss.) M.Roem.	The leaf aqueous extract inhibit	The aqueous leaf extract suppresses	Aqueous leaf extract promotes immune	Wang and Liu, 2014; Peng et al.,

		cellular entry of SARS CoV virus	NF-κB pathway and also reduce IL-6 production in LPS-treated RAW264.7 cells	responses	2019; Yang et al., 2017
Moraceae	*Broussonetia papyrifera* (L.) L'Her. ex Vent	Polyphenols from ethanol root extract markedly inhibited 3CL and PL CoV proteases. The isolated compounds exerted significant SARS-CoV PLpro inhibitory activity through noncompetitive inhibition	Broussochalcone A inhibits iNOS, by suppression of IkBα phosphorylation, IkBa degradation, NF-kB activation and iNOS expression. Flavonoid rich fraction inhibit the production of TNF-α and IL-6	The plant root ethanol extract reduced IgE-dependent passive cutaneous anaphylaxis	Park et al., 2017; Wang et al., 2012
Myrtaceae	*Syzygium aromaticum* (L.) Merr.	Higher binding affinity with viral and host macromolecular targets and other human proinflammatory mediators, SARSCoV-2 main proteases, spike, human ACE2 and furin proteins	Eugenol prevent increase in IL-4, IL-5 and the down regulation of proinflammatory cytokines IL-6 and TNFα	Eugenol found immunomodulatory activity	Maurya and Sharma, 2020; Bachiega et al., 2012; Barboza et al., 2018; Pramod et al., 2010; Dibazar et al., 2015

Paulowniaceae	*Paulownia tomentosa* Steud.	Apigenin from methanol flower extract suppressed Enterovirus 71 replication by targeting the transacting factors	Stem bark methanol extract reduced the production of IL-6 and TNF- α in LPS-stimulated RAW264.7 cells	The flower polysaccharides extracts enhanced lymphocyte proliferation, serum antibody titer and serum IFN-γ concentrations	Ji et al., 2015; Jo and Kim, 2019; Lee et al., 2018; Yang et al., 2019
Piperaceae	*Piper nigrum* L.	Higher binding affinity with viral and host macromolecular targets and other human proinflammatory mediators, SARSCoV-2 main proteases, spike, human ACE2 and furin proteins	Piperine inhibits the production of pro-inflammatory cytokines IL-1β, IL-6, IL-10 and TNFα by inhibiting NF-κB activation	It act as immunomodulator	Maurya and Sharma, 2020; Dzoyem et al., 2017; Gorgani et al., 2017
Ranunculaceae	*Cimicifuga racemosa* (L.) Nutt.	Rhizome methanol extract inhibit corona virus replication. Cimicifugin (iii) showed antiviral effect against human Respiratory Syncytial Virus	Root ethanol extract inhibited IL-6, IL-23 and TNF-α mRNA expression	The triterpenoid saponins possesses immunosuppressive	Kim et al., 2008; Guo et al., 2017; Li et al., 2006

		(RSV)			
Rutaceae	*Phellodendron chinense* C.K.Schneid	The methanol plant extract inhibit coronavirus specific porcine epidemic diarrhea virus	Methanol extract reduces release of TNF-α and IL-1β from microglia. In LPS-induced *in-vivo* model it decreases MCP-1and IL-6 in serum. It also inhibited nitric oxide synthase (iNOS), activated nuclear factor (NF)-κB and phosphorylated IκBα, and attenuated phosphorylation of mitogen-activated protein kinases (MAPKs; ERK 1/2, p38 and JNK) *in-vivo*	Polysaccharides from aqueous extract stimulate humoral immunity, macrophages and NK cells	Kim et al., 2008; Sun et al., 2019;
	Toddalia asiatica (L.) Lam.	5,6-Dihydronitidine inhibit 3CLpro	Methylene chloride and Methanol (1:1) root extract reduces carrageenin-induced acute inflammation paw oedema	Ethanol root extract showed immunomodulatory activity by inhibiting Proinflammatory cytokines	Gyebi et al., 2020; Kariuki et al., 2013; Martel et al., 2017
Theaceae	*Camellia sinensis* (L.) Kuntze	Hydrolysable tannins from leaf ethanol extract	In RAW 264.7 cells the ethanol leaf extract decreased the levels of NO, COX-2,	In immunocompromised rats aqueous leaf extract increased the level of IL-17A, IL-8, and HBD-2	Rahayu et al., 2018; Chattopadhyay et al., 2012; Gomes et al., 2014; Novilla et

		having antiviral property against influenza A by blocked the viral replication and RNA-dependent RNA polymerase	IL-6, IL-1b, and TNF-α		al., 2017; Mahmood et al., 2016
Urtiaceae	*Urtica dioica* L.	Lectin inhibit SARS-CoV infection by targeting early stages of the replication cycle or penetration and neutralizes the virus infectivity	Hydro alcoholic extract of aerial part decreased IL-6 and High Sensitive C-Reactive Protein (hs-CRP).	Flavonoid fraction and flavonoid glycosides from methanol extract of aerial part showed immunostimulatory activity	Day et al., 2009; Yohichi et al., 2011; Semalty et al., 2017; Akbay et al., 2003
Zingiberaceae	*Curcuma longa* L.	A combination of vitamin C, curcumin and glycyrrhizic acid exhibited COVID-19 Mpro inhibitions. Cucrcumin inhibited human respiratory syncytial virus replication and budding	Curcuminoids prevent leukotriene's, prostaglandins, interferon-inducible protein, TNF, IL-12 and IL-6	Aqueous extract increased NO, IL-2, IL-6, IL-10, IL-12, IFN-γ, TNF-α	Chen et al., 2020; Ashraf and Sultan, 2017; Chandrasekaran et al., 2013

	Zingiber Officinale Roscoe	6-gingerol binds at active sites of R7Y COVID-19, main protease essential for replication and reproduction of SARS-Cov-2	6-gingerol inhibits the production of proinflammatory cytokines IL-1β, IL-12, TNFα	6-gingerol possess immunomodulatory properties	Rathinavel et al., 2020; Tripathi et al., 2007; Sharifi-Rad et al., 2017
Zygophyllaceae	*Tribulus terrestris* L.	Methanol fruit extracts showed *in vivo* antiviral potential on newcastle disease virus Haemagglutination titer *in vivo* vero cell line culture. The extract exhibited enormous anti Newcastle disease virus effect in vero cell line	Tribulusamide D isolated from the hydroalcoholic extract of T. terrestris exhibited anti-inflammatory effect on lipopolysaccharide stimulated RAW 264.7 macrophages. The phytomolecule inhibited the production of LPS induced nitric oxide and prostaglandin E2, by reducing the expression of inducible nitric oxide synthase and cyclooxygenase 2 expression	Saponins isolated from the aqueous fruit extract exhbited increasing phagocytosis, stimulation of nonspecific immune response in a dose-dependent manner. Alcoholic extract of the whole plant having the effect to increase in humoral antibody titre and delayed type hypersensitivity response in a dose-dependent manner that indicating increased immune response	Tilwari et al., 2011. Lee et al., 2017. Malik et al., 2018

Table 2: Herbs derived secondary metabolites found to be effective against COVID-19 through molecular docking analysis.

Plant Family	Plant name	Antiviral	Anti-inflammatory	Immunomodulation	References
Molecular docking study					
Apocynaceae	*Nerium oleander* L.	Digitoxigenine (ix) and Calarene (x) interact with Coronavirus spike protein.	The flower aqueous extract inhibited NO production and ERK phosphorylation. Oleandrin blocked TNF-α induced activation of NF-kB.	Stimulate the cell-mediated and the humoral mediated immune systems, specifically stimulates T and B lymphocytes.	Aanouz et al., 2020; Balkan et al., 2018; Manna et al., 2000;
Acantahaceae	*Andrographis paniculata* (Burm. f.) Wall. ex Nees	Andrographolide (xxvi) inhibthe main protease of SARS-COV-2 (Mpro) through in silico studies	Andrographolide significantly reduced production of IL-1β, IL-6, CXCL-1, MCP-1	Andrographolide was reported to stimulate an innate immune response in in-vivo model. Ethanol extract induced phagocytic activity and peritoneal macrophages and Increases lymphocytes cell proliferation	Enmozi et al., 2020; Shen et al., 2002; Puri et al., 1993; Churiyah et al., 2015
Amaranthaceae	*Amaranthus tricolor* L.	Amaranthin (xxiv) may inhibit SARS-CoV-2 3CLpro activity and hence virus replication	The hydroalcohol extract of leaves showed anti-inflammatory activity in in-vivo model		Qamar et al., 2020; Bihani et al., 2013; Srivastava., 2017

Amaryllidaceae	*Allium sativum* L.	Allyl disulfide, allyl trisulfide, allyl (E)-1-propenyl disulfide, allyl methyl trisulfide, diallyl tetrasulfide, 1,2-dithiole, allyl (Z)-1-propenyl disulfide, 2-vinyl-4H-1,3-dithiine, 3-vinyl-1,2-dithiacyclohex-4-ene, carvone, trisulfide, 2-propenyl propyl, methyl allyl disulfide, diacetonalcohol, trisulfide, (1E)-1-propenyl 2-propenyl, allyl sulfide, 1-propenyl methyl disulfide, trisulfide, (1Z)-1-propenyl 2-propenyl showed inhibition of the ACE2 protein Allicin (xxv) may act as potential inhibitors of the COVID-19 Mpro	DMSO extract of Garlic powder reduced NF-κB, IL-1β, IL-6, TNF-α and diallydisulfide also significantly reduced IL-1β and TNF-α	Aqueous extract of Garlic powder increases the nucleolar activity and lymphocyte proliferation	Thuy et al., 2020; Khaerunnisa et al., 2020; Keiss et al., 2003; Zamani et al., 2011

Apiaceae	*Angelica keiskei* (Miq.) Koidz.	Nine alkylated chalcones and four coumarins exhibited 3CLpro and PLpro inhibitory activity in a dose dependent manner	The n-hexane bark extract down regulate NF-κB-dependent gene products. Compounds present in the plant showed potent inhibition of IL-6 production in TNF-α-stimulated MG-63 cell.	Xanthoangelol B, xanthoangelol C, and xanthoangelol E are immunological stimulators. *Selinidin suppress LTC4 synthesis and TNF-α production	Islam et al., 2021 Lindsay and Nadja, 2016; Kil et al., 2017
Asteraceae	*Aster tataricus* L.	The phytomolecules may inhibit 3CLpro or viral entry through binding with spike protein	Ethanol root extract decreased IL-1β, IL-6 and TNF-α level.		Zhang et al., 2020d; Rho et al., 2020
Asteraceae	*Erigeron breviscapus* (Vaniot) Hand.-Mazz.	The phytomolecules may inhibit 3CLpro or viral entry through binding with spike protein	Scutellarin reduced IL-18, and IL-1β. Breviscapine down-regulated IL-6 In-vivo		Zhang et al., 2020d; Zhu et al., 2018
Betulaceae	*Alnus japonica* (Thunb.) Steud.	Diarylheptanoids (Hirsutenone) inhibited replication of SARS-CoV PLpro by inhibiting Papain like protease.	Ethanol bark extract inhibit NO and COX-2 production. Triterpenoid present in the plant inhibit IL-1β and IL-6 levels induced by LPS in macrophage cells.	Ethanolic extract of leaves and barks of A. japonica possesses immunomodulatory activity	Demeke et al., 2021; Choi et al., 2011; Kim et al., 2005

Brassicaceae	*Isatis indigotica* Fortune	Indigo, sinigrin, aloe emodin (xxiii) and hesperetin blocked the cleavage processing of the 3CLpro	Root methanol extract inhibited TNF-α, IL-1 or IL-6 production	The root aqueous extract with DNA vaccine has adjuvant effect on the immune response against foot-and-mouth-disease-virus	Liang et al., 2020; Meng et al., 2017; Lin et al., 2005; Chen et al., 2012
Celastraceae	*Tripterygium regelii* Sprague & Takeda	Quinone-methide triterpenes celastrol, pristimerin, tingenone, iguesterin and dihydrocelastrol showed potent inhibitory activities against SARS-CoV 3CLpro			Ryu et al., 2010b
Euphorbiaceae	*Phyllanthus emblica* L.	Phyllaemblicin B (xiv) and phyllaemblinol showed binding affinity to Helicase (Nsp13). Phyllaemblicin G7 showed binding affinity to Spike protein, ACE2 protein Phyllaemblinol exhibited binding affinity to 3CLpro.	The aqueous fruit extract suppress COX-2, iNOS, IL-16, IL-6 and reduced TNF-α, IL-1β	The aqueous fruit extract enhance NK cell activity and antibody dependent cellular cytotoxicity	Yin et al., 2021; Wu et al., 2020; Wang et al., 2017; Suresh and Vasudevan, 1994

		Phyllaemblicin B found to inhibit RNA-dependent RNA polymerase			
Legumes	*Phaseolus vulgaris* L.	3,5,7,3',4',5'-hexahydroxy flavanone-3-O-beta-D-glucopyranoside have potential anti-SARS-CoV-2 property. Quercetin-3-glucuronide-7-glucoside, Quercetin 3-vicianoside, Schaftoside, Chrysoeriol 8-C-glucoside, Isosakuranetin 7-O-neohesperidoside, Delphinidin 3-O-glucoside, Petunidin 3-O-glucoside found to bind with M^{pro} and ACE2 receptors.	The navy bean or black bean flour-containing diet significantly reduced IL-1β, TNFα, IFNγ, IL-17A, and IL-9.	The lectin crude extract has immunomodulatory effect	Qamar et al., 2020; Joshi et al., 2020; Chaki and Bhattacharjee, 2016;

Magnoliaceae	*Magnolia officinalis* Rehder & EHWilson	Magnolol (xvi) showed potential PLpro inhibition.	Honokiol and magnolol inhibit PGD2, PGE2, leukotriene C4, LTB4, and thromboxane B2. Bark extracts inhibit the production of IL-6 in HGF-1 cells.	polyphenol rich aqueous extract from bark reduced serum NO, IL-6 and TNF-α, inhibiting pneumonia, decreasing lung viral titers and sensitizing IVA-induced apoptosis	Wu et al., 2020; Lin et al., 2007; Wu et al., 2011
Menispermaceae	*Tinospora cordifolia* (Willd.) Miers	Berberine (xxi), isocolumbin, magnoflorine (xxii) and tinocordiside interfere with the viral attachment and replication due to binding efficacy against surface glycoprotein and receptor binding domain and main protease	Chloroform stem extract prevented IL-6, IL-1β and PGE2	Aqueous and methanolic stem extract stimulate production of IFN-γ, TNF-α, and IL-1β Cordifolioside A and syringin possess immunomodulatory activity	Alsuhaibani and Khan, 2017; Sagar et al., 2020; Vellingiri et al., 2020; Sharma et al., 2012; Philip et al., 2018
Myricaceae	*Myrica cerifera* L.	Myricitrin (xi) showed good interaction potential with SARS-CoV-2 $3CL^{pro}$ receptor.	Myricanone down-regule the NF-κB		Qamar et al., 2020; Paul et al., 2013;

Oleaceae	*Olea Europaea* L.	Luteolin-7-glucoside (xii) and Oleuropein (xiii) appeared to have potential to act as COVID-19 Mpro inhibitors.	Oleuropein inhibit IL-1β production and down regulated iNOS, COX-2, NFKB, and JNK, and IL-6 and IL-1β	The hydroalcohol leaf extract reduced IL-1β, IL-6, IL-8,TNF-α and iNOS expression	Khaerunnisa et al., 2020; Nediani et al., 2019; Vezza et al., 2017
Oxalidaceae	*Averrhoa bilimbi* Linn.	It possesses potential inhibition of Main Protease (Mpro) by Molecular docking study	The methanol fruit extract decreased IL-1b, IL-6, TNF-a levels	Methanol fruit extracts significantly inhibited the CD18/11a expression	Khaerunnisa et al., 2020; Harun et al., 2014
Piperaceae	*Piper longum* L.	Piperolactam A (xv) interacts with Mpro and ACE2 enzyme.	Dichloromethane fraction suppress IL-1β, IL-6, and TNF-α. Fruits inhibited the release of cytokines, eosinophil infiltration in lungs.	Piperine having anti-apoptotic and restorative ability against splenic B and T cell population and IL-2 and gamma-Interferon release	Wang et al., 2017; Joshi et al., 2020; Pathak and Khandelwal, 2007;
Ranunculaceae	*Nigella sativa* L.	Nigellidine (vii) and α- Hederin (viii) showed to inhibit 3clpro/Mpro COVID-19 and 3clpro/Mpro SARS-coronavirus in an in-silico study.	The fixed oil and thymoquinone both found to down-regulate COX, 5-LO, 5-HETE and suppresses IL-6, TNFα, and NO production	The aqueous seed extract improves both cellular immunity and humoral immunity by stimulating CD4+	Salim and Noureddine, 2020; Kakepoto, 2020; Majdalawieh and Fayyad , 2015
Solanaceae	*Withania somnifera* (L.) Dunal	Withanone (xviii) block or weaken COVID-19 entry and	Aqueous root extract inhibited IL -8, IL-6, TNF-α,	A herbo mineral formulation containing aswagandha significantly	Balkrishna et al., 2020b; Gupta et al., 2014;

		its subsequent infectivity Steroidal lactones and quercetin potentially inhibited SARS COV PLpro and 3CLpro	IL-1β and IL-12	increased the CD4+ and CD8+.	Chandra et al., 2012; Sikandan et al., 2018; Leemol Davis and Girija Kuttan, 2000; Gupta et al., 2006; Trivedi et al., 2017; Das et al., 2021
Taxaceae	*Torreya nucifera* (L.) Siebold & Zucc.	Biflavone (xix), amentoflavone (xx) showed 3CLpro inhibitory effect	The leaves reduced secretion of IL-1β, IL-6, NO and PGE2		Ryu et al., 2010a; Yoon et al., 2009
Theaceae	*Camellia sinensis* (L.) Kuntze	Theaflavin-3'-gallate, Theaflavin-3,3'-digallate and tannic acid are effective against 3CLPro Isolated Theaflavin from leaves of C. sinensis exhibited inhibitory activity against SARS-COV-2 virus through binding to RNA dependent RNA polymerase	Ethanol leaf extract and epigallocatechin gallate suppressed the production of NO, COX-2, IL-6, IL-1β, and TNF-α	Hot water extract of leaves significantly increased blood leucocyte, lymphocyte count, peritoneal macrophages, spleen and thymic lymphocytes count, lung macrophages count	Chen et al., 2005; Novilla et al., 2017; Gomes et al., 2013; Sharangi, 2009; Islam et al., 2021

Zingiberaceae	*Zingiber officinale* Roscoe	6-gingerol (xvii) showed interaction with viral proteases, RNA binding protein, Spike protein Hot water extracts of fresh rhizomes inhibited viral attachment of human respiratory syncytial virus (HRSV)	Rhizome supplement reduced TNF-α, IL-6 level.	Ginger essential oil recovered the humoral immune response	Chang et al., 2013; Rathinavel et al., 2020; Maged et al., 2013; Penna et al., 2003; Carrasco et al., 2009;
Zygophyllaceae	*Tribulus terrestris* L.	Cinnamic amides and ferulic acid showed inhibitory activity against PLpro.	Tribulusamide D inhibited the production of iNOS, PGE2 and reduced the expression of IL-6, IL-10 and TNF- α	Seed aqueous and ethanol extracts increases IL-6 level	Song et al., 2014; Wu et al., 1999; Lee et al., 2017; Abdelrazek et al., 2018